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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

HUTSON, RICHARD G

ART UNIT

PAPER NUMBER

1652

DATE MAILED: 07/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/979,518

Applicant(s)

MEIS, JUDITH E

Examiner

Richard G. Hutson

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 39-55 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 39-55 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. ____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|--|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>11/2001;5/2002</u> | 6) <input type="checkbox"/> Other: ____ |

DETAILED ACTION

Applicants cancellation of claims 1-38 and the addition of new claims 39-58, in the paper of 11/16/2001, is acknowledged. Claims 39-58 are present and at issue for examination.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper."

Applicants filing of information disclosure statements filed on 11/16/2001, and 5/14/2002 are acknowledged. Those references considered have been initialed.

Claim Objections

Claims 52 are objected to because of the following informalities:

Claim 52 is objected to for the use of abbreviations. It is suggested that the first time an abbreviation is used in the claims it be written out in full.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

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The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 48 is indefinite in that it is confusing in the recitation "(MASTERAMP PCR ENHANCER) It is unclear what this recitation is or its relationship to "betaine".

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 39-50 and 51-55 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 39-50 and 51-55 are directed to all possible methods of preparing a cDNA molecule or amplifying a nucleic acid molecule comprising mixing any RNA template with any thermostable DNA polymerase from *B. stearothermophilus* and incubating under conditions sufficient to amplify a DNA molecules.

The specification, however, only provides the representative methods of use of DNA polymerases isolated from *B. stearothermophilus* strain ATCC number 12980, encompassed by these claims. There is no disclosure of any particular structure to function/activity relationship in the polymerases necessary to practice the claimed

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methods. The specification also fails to describe additional representative species of these enzymes by any identifying structural characteristics or properties other than the activities recited in claims 39, for which no predictability of structure is apparent. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 39-50 and 51-55 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the claimed amplification /synthesis methods using the DNA polymerase from strain ATCC No. 12980 provided it was made available to one of skill in the art, does not reasonably provide enablement for the claimed methods of amplification/synthesis using any DNA polymerase from any *B. stearothermophilus*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of

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direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 39-50 and 51-55 are so broad as to encompass any the method of amplification/synthesis using any DNA polymerase from any *B. stearothermophilus*. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of enzymes necessary to practice the claimed methods, including all *B. stearothermophilus* DNA polymerases and variants thereof. The claims rejected under this section of U.S.C. 112, first paragraph, do not place any structural limits on the necessary enzymes. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to those methods using the DNA polymerase from strain ATCC No. 12980 provided it was made available to one of skill in the art.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the polymerases necessary to practice the claimed methods, and the positions within a

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protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all methods of use of any modifications and fragment of any *B. stearothermophilus* DNA polymerase, because the specification does not establish: (A) regions of the protein structure which may be modified without effecting polymerase activity; (B) the general tolerance of *B. stearothermophilus* DNA polymerase to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue of a *B. stearothermophilus* DNA polymerase with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. Because of this lack of guidance, the extended experimentation that would be required to determine which substitutions would be acceptable to retain the *B. stearothermophilus* DNA polymerase activity necessary to practice the claimed methods and the fact that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (e.g., see Ngo et al. in *The Protein Folding Problem and Tertiary Structure Prediction*, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), it

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would require undue experimentation for one skilled in the art to arrive at the majority of those methods of use of any *B. stearothermophilus* DNA polymerase.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including method of use of any number of amino acid modifications of any *B. stearothermophilus* DNA polymerase. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 39-41, 43-47 and 49-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Swaminathan et al. (U.S. Patent No. 5,830,714, See IDS) and Spargo et al. (See IDS).

Swaminathan et al. teach reverse transcriptase products from *B. stearothermophilus* and methods of preparing a cDNA molecule from a RNA template

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and amplifying a nucleic acid comprising mixing a RNA template with B
stearothermophilus DNA polymerase comprising reverse transcriptase activity in the
presence of various concentrations of magnesium and incubating under conditions
sufficient to amplify/synthesize a DNA molecule. Swaminathan et al. further teach that
the above methods comprise the removal of the 5'-3' activity and compositions.

Spargo et al. teach various methods of thermophilic strand displacement
amplification of DNA including amplification with the substantial absence of manganese
ions.

One of ordinary skill in the art at the time of filing would have been motivated to
alter the various conditions taught by Swaminathan et al. used for
synthesis/amplification of nucleic acid products as a means of increasing the efficiency
of product produced. Such methods involve the alteration of both magnesium and
manganese concentrations. The reasonable expectation of success comes from the
high degree of expertise in the art of polymerase chain amplification reactions and the
use of DNA/RNA polymerases to synthesize isolated nucleic acid products and the
results of both Swaminathan et al. and Spargo et al.


Thus claims 39-41, 43-47 and 49-55 are made obvious over Swaminathan et al.
and Spargo et al.

Any inquiry concerning this communication or earlier communications from the
examiner should be directed to Richard G. Hutson whose telephone number is (571)
272-0930. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

A handwritten signature in black ink, appearing to read 'Richard G. Hutson', with a long horizontal line extending to the right.

Richard G Hutson, Ph.D.
Primary Examiner
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